Remarks

Claims 1-64 are pending in this application. Claims 3, 5-7, 9, 11, 14-16, 19, 21, 24, 26-28, 30, 32, 35-37, 40, 42, and 44-64 have been withdrawn from consideration as unelected subject matter. Therefore, claims 1, 2, 4, 8, 10, 12, 13, 17, 18, 20, 22, 23, 25, 29, 31, 33, 34, 38, 39, 41, and 43 are currently under consideration.

Claims 4 and 13 were amended to clarify that counts are entered in the input layer. Support is found at claim 1. Claims 13 and 34 were amended to clarify the meaning of ROC. Support is found at page 9, line 1. No new matter was added to the application by virtue of these amendments.

A Petition Under 37 C.F.R. § 1.136(a) for a three-month extension of time and the associated fee are enclosed with this paper.

I. Response to Objection to Specification

The specification was objected to for containing an embedded hyperlink or other form of browser-executable code. The specification has been amended at the paragraphs beginning at page 20, line 1, and page 26, line 19, for deleting the hyperlink or other form of browser-executable code. Withdrawal of the objection is respectfully requested.

The specification was also objected for allegedly failing to provide antecedent basis for claimed subject matter. More particularly, the Office Action alleged that the specification fails to provide antecedent basis for "at least one hidden layer comprises from about 4 to about 16 hidden nodes" in claims 8 and 29, "using a back-algorithm without a momentum term" in claims 12 and 33, and "using a binary threshold function with a cutoff in the range of about 0.01-0.50" in claims 18 and 39.

Support for the objected subject matter of claims 8 and 29 is found at page 20, lines 12-13. Support for the objected subject matter of claims 12 and 33 is found at page 21, lines 3-4. Applicants respectfully disagree with the Office Action's allegation that this portion of the specification fails to provide adequate support for the claimed subject matter. However, Applicant's have amended the specification at the paragraph beginning at page 20, line 15 to remove all doubt. The specification was amended at the paragraph beginning at page 25, line 8, to include a statement that the binary threshold function has a cutoff in the range of about 0.01-0.50. Support for this amendment is found at claims 18 and 39.

No new matter is added to the application by virtue of these amendments.

In view of the above, withdrawal of the objections to the specification is respectfully requested.

II. Response to Objections to Claims

Claims 20 and 41 were objected to under 37 C.F.R. § 1.75(c) for allegedly being of improper dependent form for allegedly failing to further limit the subject matter of a previous claim.

With respect to claim 20, the Office Action alleged that claim 1, from which claim 20 depends, "is drawn to a method of predicting antisense activity by employing an single artificial network. Claim 20 is more broadly drawn to predicting antisense activity by employing multiple (at least two or more) artificial neural networks. As such, claim 20 fails to further limit the subject matter of claim 1."

First, claim 1, in pertinent part, is drawn to a method for predicting antisense activity comprising developing an artificial neural network. This claim is not limited to use of a single artificial neural network, as alleged in the Office Action. The transition term "comprising" is an inclusive or open-ended term that does not exclude additional, unrecited elements or method steps (page 10, lines 13-16; *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 71 USPQ2d 1837, 1841-8142 (Fed. Cir. 2004)). Therefore,

claim 1 does not exclude use of more than one artificial neural network.

Second, claim 1 uses the indefinite article "an" for modifying "artificial neural network." As defined in the specification at page 10, lines 9-10, the singular article "an" includes plural referents unless the context clearly dictates otherwise. The context does not clearly dictate otherwise, thus, plural referents are included.

Third, according to conventional rules of claim construction, use of an indefinite article in a patent claim together with an open-ended transitional phrase means "one or more." On this subject the Federal Circuit stated:

> This court has repeatedly emphasized that an indefinite article "a" or "an" in patent parlance carries the meaning of "one or more" in open-ended claims containing the transition phrase "comprising." Unless the claim is specific as to the number of elements, the article "a" receives a singular interpretation only in rare circumstances when the patentee evinces a clear intent to so limit the article. Under this conventional rule, the claim limitation "a," without more, requires at least one.

KCJ Corp. v. Kinetic Concepts, Inc., 223 F.3d 1351, 1356, 55 USPQ2d 1835, 1839 (Fed. Cir. 2000) (citations omitted); *Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 57 USPQ2d 1953 (Fed. Cir. 2001).

Fourth, the allegation that claim 20 is broader than claim 1 is false. As explained above, claim 1 can include "one or more" artificial neural networks. Claim 20 restricts the scope of claim 1 by requiring that the predicted antisense activity of the artificial neural network of claim is combined with a predicted antisense activity of at least one other artificial neural network. Claim 20 is narrower than claim 1 because use of only one artificial neural network is precluded.

For these reasons, the objection to claim 20 is flawed, and withdrawal of the objection is respectfully requested. The objection to claim 41 is flawed for similar reasons, and withdrawal of that objection is also respectfully requested.

III. <u>Response to Rejection Under 35 U.S.C. § 112, First Paragraph</u>

Claims 4 and 25 were rejected for allegedly failing to comply with the enablement requirement of Section 112, first paragraph.

Claims 4 and 25 have been amended to clarify that the input data are counts. In view of these amendments, it is respectfully submitted that these claims comply with the enablement requirement of Section 112, first paragraph. Withdrawal of the rejections is respectfully requested.

IV. Response to Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 13, 18, 34, and 39 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

Claims 13 and 34 were rejected for use of the term "ROC." Applicants respectfully submit that this term is defined in the specification and is also well known in the applicable art. Therefore, a person skilled in the art would understand the metes and bounds of the claim, and the claim is not indefinite. However, to advance the prosecution of the application and receive an early allowance of claims, Applicants have amended claims 13 and 34 to include the term "receiver operating characteristic." Accordingly, withdrawal of the rejection is respectfully requested.

Claims 18 and 39 were rejected for use of the range "0.01-0.50." The Office Action alleged that this term is relative and use of this term renders the claims indefinite. In particular, the Office Action appears to request that units be appended to allegedly make the term definite. It is respectfully submitted that the binary threshold function uses unitless indicia. Therefore, it is not possible to append units. In *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir.

1986) (citing *Shatterproof Glass Corp. v. Libbey Owens Ford Co.*, 225 U.S.P.Q. 634, 641 (Fed. Cir. 1985)), it was stated:

> [I]f the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more.

Thus, whether a claim is in compliance with the second paragraph of § 112 requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification. A person skilled in this particular art would understand that the binary threshold function indicia are unitless. Thus, claims 18 and 39 are in compliance with Section 112, second paragraph, and withdrawal of the rejection is respectfully requested.

V. Response to Rejections Under 35 U.S.C. § 103

A. Standards Under 35 U.S.C. § 103

Before responding directly to the issues raised by the Office Action under Section 103, the legal foundation for sustaining such a rejection will be reviewed. Briefly, an applicant for a patent is entitled to the patent unless the application fails to meet the requirements established by law. 35 U.S.C. §§ 102, 103. It is the Patent Office's duty to issue a patent or establish that the applicant is not entitled to a patent under the law. *In re Warner*,

154 USPQ 173, 177 (CCPA 1967), *cert. denied*, 389 U.S. 1057 (1968). Thus, the burden is on the Patent Office to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). If no *prima facie* case of obviousness is established, then a rejection under Section 103 cannot properly be sustained. *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). If the Patent Office establishes a *prima facie* case of obviousness, then the burden of production shifts to the applicant to provide appropriate rebuttal, although the burden of persuasion always remains with the Patent Office. *Id.* Such rebuttal may include arguments, amendments, and/or presentation of objective indicia of nonobviousness. However, such objective indicia are always relevant to a determination of nonobviousness whether or not a *prima facie* case of obviousness has been established. *Stratoflex Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1987). To establish a *prima facie* case of obviousness, the Patent Office must show all of the limitations of the claimed invention in the prior art. *In re Ehrreich*, 200 U.S.P.Q. 504, 509-11 (C.C.P.A. 1979). The subject matter of the invention must be considered as a whole and through the eyes of a hypothetical person of ordinary skill, not expert skill, in the relevant art at the time the invention was made. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, 199 (Fed.

Cir. 1983). References must also be considered as a whole, including subject matter that teaches away from the invention as well as subject matter that suggests the invention, and not for their isolated teachings. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 227 U.S.P.Q. 657, 669 (Fed. Cir. 1985). References may be combined if there is a suggestion, motivation, or incentive in the prior art to make such a combination. *In re Dillon*, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990) (en banc); *In re Jones*, 21 U.S.P.Q.2d 1941, 1943-44 (Fed. Cir. 1992). It is not permissible to use hindsight to pick and choose among isolated teachings in the art after first having read Applicant's application to learn the pattern of the invention. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Finally, all the facts in evidence are evaluated, and patentability is determined on the totality of the record. *In re Corkill*, 226 USPQ 1005, 1008 (Fed. Cir. 1985). Factual determinations made by the PTO must be based on a preponderance of the evidence, and legal conclusions must be correct. *In re Caveny*, 226 USPQ 1, 3 (Fed. Cir. 1985).

Pursuant to established legal authority, patentability under 35 U.S.C. § 103 requires a four-step analysis, which involves determining (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed inventions, (3) the level of skill in the art, and (4) the objective evidence of

nonobviousness that may have been presented. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 311, 314 (Fed. Cir. 1983). After all of these factors have been considered, the ultimate legal conclusion on the issue of obviousness must be reached. With the above background in mind the rejections under 35 U.S.C. § 103 will be discussed.

B. Argument

Claims 1, 2, 8, 10, 12, 17, 22, 23, 29, 31, 33, 38, and 43 were rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over O. Matveeva et al., Prediction of antisense oligonucleotide efficacy by in vitro methods, 16 Nature Biotechnology 1374-1375 (1998) ("Matveeva") in view of Wu et al., Back-propagation and counter-propagation neural networks for phylogenetic classification of ribosomal RNA sequences, 22 Nucleic Acids Res. 4291-4299 (1994) ("Wu").

The only relationship between Matveeva and the present application is that both deal with predicting antisense oligonucleotide efficiency. Matveeva and the present application address the same problem in that few oligonucleotides are efficient and it is too expensive to test many oligonucleotides for finding the few that are efficient. However, the solutions to this problem

presented by Matveeva and by the present application are very different.

Matveeva suggested using *in vitro* experiments for predicting *in vivo* antisense oligonucleotide efficiency. Matveeva showed that a correlation existed between efficiencies of antisense oligonucleotides *in vitro* and *in vivo. In vitro* experiments are cheaper that *in vivo* experiments, so it made sense to try *in vitro* experiments first, to pick efficient antisense oligonucleotides from those *in vitro* experiments, and finally to perform the expensive *in vivo* experiments.

However, computer modeling is much cheaper than *in vitro* experiments. Thus, the present application claims a method of searching for efficient antisense oligonucleotides using neural networks, which is a way of performing computer modeling of the problem. Computer modeling and *in vitro* modeling are very different. By analogy, just because somebody could build a small model of a house does mean that same person could make a computer model of the house. Computer modeling and *in vitro* modeling require different knowledge and different tools.

Wu used neural networks as a tool for analyzing ribosomal RNA phylogenies. However, the problem of ribosomal RNA phylogenetic analysis and the problem of prediction of antisense oligonucleotide efficiency are unrelated. Neural networks have been used for

solving many problems in molecular biology. However, having a problem and knowing how to use a tool to solve a different problem do not mean that it would be obvious to solve the first problem with the tool. In the present case, the inputs and outputs of Wu and the present invention are absolutely different, as are the functions that relate the inputs and outputs. The only similarities between We and the present invention are neuronal networks and RNA. Otherwise, they are vastly different.

Further, Wu stated at page 4298 that it was not obvious that the neural network approach would be applicable and feasible in going from protein sequence phylogenetic classification to nucleic acid sequence phylogenetic classification. Both of these functions are one-to-one matching processes, but if Wu did not think it was obvious that two similar classification processes could be carried out using neural networks, then it certainly would not be obvious that one could successfully carry out a motif-to-motif functional classification using a neural network.

Moreover, Wu suggested only that the neural network approach should be applicable for nucleic acid sequence identification. Nowhere did Wu suggest that this approach should be applicable for nucleic acid functional prediction. Matching items by appearance using discrete components and prediction of functionality by gauging the presence of well-defined motifs are very different

things, and it is not obvious that any given process will work to do both.

To underscore these differences, it should be noted that the identification matching presented by Wu for protein and RNA sequences works with very high accuracy (90% in Wu et al., Protein classification artificial neural system, 1 Protein Sci. 667-677 (1992), and 100% in Wu). If it were obvious that such a process would work at the level of functional classification, then one would expect an equally impressive accuracy. However, accuracy found by the inventors was about 55%. Although this is a huge improvement over prior methods of identifying functionally effective oligonucleotide sequences, it suggests that it was not easy or obvious to apply neural networks to the problem.

Still further, the combination of Matveeva and Wu fails to disclose or suggest each and every limitation of the presently claimed invention. For example, the cited references fail to disclose or suggest (1) mapping sequence motifs of a preselected length found in the sequence data contained in the database, entering counts for each of the sequence motifs in selected input nodes of the input layer, and entering activity data correlated with the counts of the sequence motifs, (2) training the artificial neural network having the counts entered in the input layer such that the artificial neural network produces an output in the output

layer upon entry of sequence motif counts, wherein the output comprises a measure of predicted activity correlated with sequence motif counts for a test oligonucleotide, (3) mapping sequence motifs of the preselected length present in a nucleotide sequence of a test oligonucleotide complementary to at least a portion of the selected RNA, determining counts of the mapped sequence motifs, and entering counts of the sequence motifs present in the nucleotide sequence of the test oligonucleotide in the input layer of the artificial neural network, and (4) obtaining output of the predicted antisense activity of the test oligonucleotide for down-regulating expression of the selected RNA. For this reason, a *prima facie* case of obviousness has not been established.

Finally, the present rejection is basically an argument that it would be obvious to try or obvious to experiment with neural networks to arrive at a method for predicting efficiency of antisense oligonucleotides. "Obvious to experiment" or "obvious to try" is not a proper standard for making a determination under Section 103. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). The fact that Wu discusses using neural networks for analyzing ribosomal RNA phylogenies does not show obviousness of the present invention, because Wu does not suggest how that end might be accomplished. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 91 (Fed. Cir. 1986). Following the

teachings of Wu, there would not be a reasonable expectation of success of making the present invention. Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 18 U.S.P.Q.2d 1016, 1022 (Fed. Cir. 1991); *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). If obvious to try was a proper standard for determining obviousness of an invention, then virtually no inventions involving recombinant DNA methods or neural networks would be patentable because it is so often obvious to try to use them for inventions involving diagnostics, pharmaceuticals, genetics, and the like. For these reasons, it is respectfully submitted that the present invention is not obvious under § 103.

For all of these reasons, it is respectfully submitted that a *prima facie* case of obviousness has not been established with respect to the presently claimed invention. Therefore, withdrawal of the rejection is respectfully requested.

VI. Conclusion

Should the Examiner deem it advisable to conduct a telephone interview for any reason, the undersigned attorney would be most agreeable to receiving a telephone call to expedite the prosecution of the application.

For the reasons given above, Applicants respectfully request reconsideration and allowance of Claims 1, 2, 4, 8, 10, 12, 13, 17,

18, 20, 22, 23, 25, 29, 31, 33, 34, 38, 39, 41, and 43 and passage of this application to issue.

DATED this 25th day of November, 2005.

Respectfully submitted,

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